



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/727,349	11/30/2000	Dean L. Engelhardt	Enz-52 (D1)	3143

28170 7590 12/06/2002

ENZO DIAGNOSTICS, INC.
C/O ENZO BIOCHEM INC.
527 MADISON AVENUE 9TH FLOOR
NEW YORK, NY 10022

EXAMINER

CHAKRABARTI, ARUN K

ART UNIT

PAPER NUMBER

1634

DATE MAILED: 12/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No. 09/727,349	Applicant(s) Engelhardt
Examiner Arun Chakrabarti	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on May 28, 2002.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-90 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-51 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims 52-90 are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. _____.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

4) Interview Summary (PTO-413) Paper No(s). _____

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

5) Notice of Informal Patent Application (PTO-152)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

6) Other: *Detailed Action*

Art Unit: 1634

DETAILED ACTION

Claim Rejections - 35 U.S.C. § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-6, 8-9, 14-15, 18-21, 26 and 28-29 are rejected under 35 U.S.C. 102 (b)

as being anticipated by Kacian et al. (U.S. Patent 5,399,491) (March 21, 1995).

Kacian et al teach an in vitro process for producing more than one copy of a specific nucleic acid, the process being independent of a requirement for the introduction of an intermediate structure for the production of the specific nucleic acid (Abstract and Figure 1J and Column 17, lines 34-38), the process comprising the steps of :

a) providing a nucleic acid sample containing or suspected of containing the sequence of the specific nucleic acid (Abstract, Figure 1J and Column 17, lines 34-38);

b) contacting the sample with a mixture comprising :

(I) nucleic acid precursors (Figure 1J and Column 17, lines 34-38),

(ii) one or more specific nucleic acid primers each of which is complementary to a distinct sequence of the specific nucleic acid (Figure 1J and Column 17, lines 34-38), and

Art Unit: 1634

(iii) an effective amount of a nucleic acid producing catalyst (Figure 1J and Column 17, lines 34-38); and

c) allowing the mixture to react under isostatic conditions of temperature, buffer and ionic strength, thereby producing more than one copy of the specific nucleic acid (Figure 1J and Column 17, lines 34-38 and Abstract).

Kacian et al teach an in vitro process wherein the specific nucleic acid is single-stranded (Figure 1J and Column 17, lines 34-38).

Kacian et al teach an in vitro process wherein the specific nucleic acid is ribonucleic acid.(Figure 1J).

Kacian et al teach an in vitro process wherein the specific nucleic acid is in solution (Column 25, lines 44-60).

Kacian et al teach an in vitro process further comprising the step of treating the specific nucleic acid with a blunt-end promoting restriction enzyme (Figure 1J).

Kacian et al teach an in vitro process wherein the specific nucleic acid is isolated prior to the contacting step (b) (Figure 1J).

Kacian et al teach an in vitro process wherein the captured nucleic acid is carried out by restriction enzyme (Figure 1J).

Kacian et al teach an in vitro process wherein the specific nucleic acid primers is deoxyribonucleic acid (Figure 1J).

Art Unit: 1634

Kacian et al teach an in vitro process wherein the specific nucleic acid primers contain no more than five complementary base pairs and comprise from about 5 to 100 nucleotides (Column 24, lines 52-63).

Kacian et al teach an in vitro process wherein the nucleic acid producing catalyst is selected from DNA polymerase and reverse transcriptase (Figure 1J).

Kacian et al teach an in vitro process further comprising the step (d) of detecting the product produced in step c) (Figures 6a and 6b).

Kacian et al teach an in vitro process wherein the detecting step is carried out by means of incorporating into the product a labeled primer (Figures 6a and 6b).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

Art Unit: 1634

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-9, 14-15, 18-21, 26 and 28-29 are rejected under 35 U.S.C. 103 (a) over Kacian et al. (U.S. Patent 5,399,491) (March 21, 1995) in view of Bernstein et al. (U.S. Patent 6,183,961 B1) (February 6, 2001).

Kacian et al teach the method of claims 1-6, 8-9, 14-15, 18-21, 26 and 28-29 as described above.

Kacian et al do not teach the process wherein the isolation of specific nucleic acid is carried out by means of sandwich capture.

Bernstein et al. teach the process wherein the isolation of specific nucleic acid is carried out by means of sandwich capture. (Column 16, lines 52-56).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the sandwich capture of Bernstein et al. into the method of Kacian et al ., since Bernstein et al. state, “For example, sandwich assays are commercially useful hybridization assays for detecting or isolating nucleic acid sequences (Column 16, lines 52-54).” An ordinary practitioner would have been motivated to combine and substitute the sandwich capture of Bernstein et al. into the method of Kacian et al ., in order to achieve the express advantages , as noted by Bernstein et al., of an assay which is commercially useful hybridization assay for detecting or isolating nucleic acid sequences.

Art Unit: 1634

5. Claims 1-6, 8-9, 14-15, 18-21, 26 , 28-35, and 39-42 are rejected under 35 U.S.C. 103 (a) over Kacian et al. (U.S. Patent 5,399,491) (March 21, 1995) in view of Jones (U.S. Patent 6,190,889 B1) (February 20, 2001).

Kacian et al teach an in vitro process of claims 1-6, 8-9, 14-15, 18-21, 26 and 28-29 as described above including the enzyme ribonuclease H.

Kacian et al do not teach an in vitro process for producing more than one copy of a specific nucleic acid, the products being substantially free of any primer-coded sequences by using chemically modified primers and removing substantially or all primer-coded sequences from the product produced in step to regenerate a primer binding site, thereby allowing a new priming event to occur and producing more than one copy of the specific nucleic acid.

Jones teaches an in vitro process for producing more than one copy of a specific nucleic acid, the products being substantially free of any primer-coded sequences using chemically modified deoxyribonucleic acid primers and removing substantially or all primer-coded sequences from the product produced in step to regenerate a primer binding site, thereby allowing a new priming event to occur and producing more than one copy of the specific nucleic acid (Abstract and Claim 1).

Kacian et al do not teach an in vitro process wherein the removing is carried by digestion with an enzyme.

Jones teaches an in vitro process wherein the removing is carried by digestion with an enzyme.(Claims 1 and 2).

Art Unit: 1634

Kacian et al do not teach an in vitro process wherein a primer binding site is regenerated, thereby allowing a new priming event to occur and producing more than one copy of the specific nucleic acid.

Jones teaches an in vitro process wherein a primer binding site is regenerated, thereby allowing a new priming event to occur and producing more than one copy of the specific nucleic acid. (Column 42, line 46 to column 43, line 31).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method for removing primer sequences of Jones into the method of Kacian et al., since Jones states, "Thus, the invention pertains to novel methods for generating staggered templates and for iterative and regenerative DNA sequencing as well as to methods for automated DNA sequencing (Column 4, lines 37-40)." An ordinary practitioner would have been motivated to combine and substitute the method for removing primer sequences of Jones into the method of Kacian et al.. in order to achieve the express advantages , as noted by Jones., of an invention that pertains to novel methods for generating staggered templates and for iterative and regenerative DNA sequencing as well as to methods for automated DNA sequencing .

6. Claims 1-6 and 8-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kacian et al. (U.S. Patent 5,399,491) (March 21, 1995) in view of Jones (U.S. Patent 6,190,889

Art Unit: 1634

B1) (February 20, 2001) further in view of Ward et al. (U.S. Patent 4,711,955) (December 8, 1987).

Kacian et al in view of Jones teach the in vitro process of claims 1-6, 8-9, 14-15, 18-21, 26 , 28-35, and 39-42 as described above.

Kacian et al in view of Jones do not teach the process wherein at least one modified nucleotide or nucleotide analog selected from cytidine 5'-triphosphate or deoxy cytidine 5'-triphosphate.

Ward et al teach the process wherein at least one modified nucleotide or nucleotide analog selected from cytidine 5'-triphosphate or deoxy cytidine 5'-triphosphate (Column 3, lines 20-39 and Examples 3 and 4).

Kacian et al in view of Jones do not teach the process wherein the analog is modified on the sugar.

Ward et al teach the process wherein the analog is modified on the sugar (Abstract and Column 3, lines 20-39).

Kacian et al in view of Jones do not teach the process wherein the analogs comprise from about 1 to about 200 nucleotide.

Ward et al. teaches the process wherein the analogs comprise from about 1 to about 200 nucleotide. (Column 5, line 1 to Column 6, line 32).

Kacian et al in view of Jones do not teach the process wherein the base sequences are linked together by other than a phosphodiester bond.

Art Unit: 1634

Ward et al. teaches the process wherein the base sequences are linked together by other than a phosphodiester bond. (Claim 8).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the modified nucleotide or nucleotide analog of Ward et al. into the nucleic acid sequence amplification method of Kacian et al in view of Jones, since Ward et al. state, "The interaction between modified nucleotides and specific proteins can be utilized as an alternative to radioisotopes for the detection and localization of nucleic acid components in many of the procedures currently used in biomedical and recombinant-DNA technologies. Methods employing these modified nucleotide-protein interactions have detection capacities equal to or greater than procedures which utilize radioisotopes and they often can be performed more rapidly and with greater resolving power. These new nucleotide derivatives can be prepared relatively inexpensively by chemical procedures which have been developed and standardized as discussed more fully hereinafter. More significantly, since neither the nucleotide probes of this invention nor the protein reagents employed with them are radioactive, the compounds can be prepared, utilized and disposed of without the elaborate safety procedures required for radioisotopic protocols. Moreover, these nucleotide derivatives are chemically stable and can be expected to have functional shelf-lives of several years or more. Finally, these compounds permit the development of safer, more economical, more rapid, and more reproducible research and diagnostic procedures (Column 2,

Art Unit: 1634

line 59 to column 3, line 17)." An ordinary practitioner would have been motivated to combine and substitute the modified nucleotide or nucleotide analog of Ward et al. into the nucleic acid sequence amplification method of Kacian et al in view of Jones , in order to achieve the express advantages, as noted by Ward et al, of a method which permit the development of safer, more economical, more rapid, and more reproducible research and diagnostic procedures.

7. Claims 1-6 and 8-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kacian et al. (U.S. Patent 5,399,491) (March 21, 1995) in view of Jones (U.S. Patent 6,190,889 B1) (February 20, 2001) further in view of Ward et al. (U.S. Patent 4,711,955) (December 8, 1987) further in view of Dahlberg et al. (U.S. Patent 5,871,911) (February 16, 1999).

Kacian et al. in view of Jones further in view of Ward et al. teach the method of claims 1-46 as described above.

Kacian et al. in view of Jones further in view of Ward et al do not teach one or more specific unmodified primers comprising at least one non-complimentary sequence to a distinct sequence of the specific nucleic acid, such that upon hybridization to the specific nucleic acid at least one loop structure is formed.

Dahlberg et al teach one or more specific unmodified primers comprising at least one non-complimentary sequence to a distinct sequence of the specific nucleic acid, such that upon hybridization to the specific nucleic acid at least one loop structure is formed. (Figure 3, Column 6, line 60 to Column 7, line 5).

It would have been *prima facie* obvious to one having ordinary skill in the art at

Art Unit: 1634

the time the invention was made to combine and substitute the primer having loop structure of Dahlberg et al. into the method of Kacian et al. in view of Ward et al ., since Dahlberg et al. state, “In this case, the pilot oligonucleotide has a 3' terminal hairpin that acts as an integral primer. The looped end of the hairpin may be of a specific sequence called a tetra-loop, which confers extraordinary thermostability on the stem-loop structure (Column 6, lines 61-65).” An ordinary practitioner would have been motivated to combine and substitute the primer having loop structure of Dahlberg et al. into the method of Kacian et al. in view of Ward et al . in order to achieve the express advantages , as noted by Dahlberg et al., of a looped end primer which confers extraordinary thermostability on the stem-loop structure.

Response to Arguments

8. Applicant's arguments filed May 28, 2002 have been fully considered and 112 (second paragraph) rejection has been withdrawn but they are not persuasive.

Applicant argues that 102(b) rejection based on Kacian reference should be withdrawn because Kacian has an extra and additional step of an artificial RNA polymerase promoter sequence to synthesize multiple copies of a target organism. This argument is not persuasive, especially in the presence of “comprising” language of the instant claims, any additional step(s) or material(s) can be added to the instant invention and any prior art describing such additional step(s) or material(s) will be appropriately applicable for an 102(b) rejection. In view of this argument , 102(b) rejection is hereby appropriately maintained.

Art Unit: 1634

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant argues that there is no motivation to combine the references. This argument is not persuasive especially in the presence of strong motivation provided by Bernstein et al. since Bernstein et al. state, "For example, sandwich assays are commercially useful hybridization assays for detecting or isolating nucleic acid sequences (Column 16, lines 52-54)." The same logic is applicable for the motivation of other combinatory references.

Applicant argues that 103(a) rejection based on Jones reference should be withdrawn because Jones has an extra and additional step of an artificial primer binding site and an artificial restriction enzyme site. This argument is not persuasive, especially in the presence of "comprising" language of the instant claims, any additional step(s) or material(s) can be added to the instant invention and any prior art describing such additional step(s) or material(s) will be appropriately applicable for an 103(a) rejection. In view of this argument , 103(a) rejection based on Jones reference is hereby appropriately maintained.

Applicant argues that Jones reference does not teach the generation of products that are substantially free of any primer-coded sequences of the claimed invention. Applicant argues that the word "free of any primer-coded sequences " was not found in Jones reference. Applicant argues that because jones has a preferred embodiment of primer-labeled detection of nucleic

Art Unit: 1634

acids, Jones is limited to the preferred embodiment. This argument is not persuasive. As MPEP 2123 states “Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 169 USPQ 423 (CCPA 1971).” MPEP 2123 also states “A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 10 USPQ2d 1843 (Fed. Cir. 1989).” It is clear that simply because Jones has a preferred embodiment, this embodiment does not prevent the reference from suggesting broader embodiments in the disclosure and that this does not constitute a teaching away. Although Jones reference uses primer-labeled detection of nucleic acid sequences, the property of generation of products that are substantially free of any primer-coded sequences is inherently present in this chemically and structurally identical molecule. For example, Jones teaches such generation of products that are substantially free of any primer-coded sequences (Column 35, lines 23-42). Moreover, MPEP 2111 states, “Claims must be given their broadest reasonable interpretation. During patent examination, the pending claims must be “given the broadest reasonable interpretation consistent with the specification”. Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than it is justified. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969).” In this case, any supports or beads of polyacrylamide under any suitable conditions can be used for gel electrophoresis.

Art Unit: 1634

Applicant also argues that there is no reasonable expectation of success to combine the references. With regard to the “lack of reasonable expectation of success ” argument, The MPEP 2143.02 states, “Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart* , 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also *Amgen, Inc. v. Chugai Pharmaceutical Co.* , 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); *In re O'Farrell* , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.”

Art Unit: 1634

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Dahlberg reference of the enabling methodology, the suggestion to modify the prior art, and evidence that a number of different hybridizations to the specific nucleic acids to form several different loop structure were actually experimentally studied and found to be functional (Figure 3 and Column 6, line 60 to Column 7, line 5). This evidence of functionality trumps the attorney arguments, which argues that Dahlberg reference is an invitation to research, since Dahlberg steps beyond research and shows the functional product.

In view of the response to arguments, all 102(b) and 103(a) rejections are hereby properly maintained.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

Art Unit: 1634

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703) 308-1152. Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located In Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published In the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Chakrabarti

Patent Examiner

Art Unit 1634

December 2, 2002


W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600